UPVG0005-101 (H1237) **133172-00511**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of: **David B. Weiner**

Confirmation No: **2356**

Serial No: **10/734,024** Group Art Unit: **1648**

Filed: **December 11, 2003** Examiner:**Louise Wang Zhiying Humphrey**

For: **COMPOSITIONS AND METHODS FOR THE ABROGATION OF CELLULAR PROLIFERATION UTILIZING THE HUMAN IMMUNODEFICIENCY VIRUS VPR PROTEIN**

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPELLANTS' APPEAL BRIEF PURSUANT TO 37 CFR §41.37

Appellants hereby submit one copy of the present Appeal Brief to the Board of Patent Appeals and Interferences ("the Board") in response to the Final Rejection, dated October 31, 2006, in connection with the above-identified application. A Notice of Appeal was timely filed April 30, 2007. The period for filing the Appeal Brief has been extended, by enclosure of a petition and payment of the appropriate fee, to and through November 30, 2007.

Appellants respectfully submit that this brief complies with 37 C.F.R. § 41.37. This brief contains the items required by 37 C.F.R. § 41.37, under appropriate headings, and an authorization to charge the fee set forth in 37 C.F.R. § 41.20(b)(2).

(i) Real Party in Interest

The real party in interest in the above-identified patent application is the assignee, The Trustees of the University of Pennsylvania of Philadelphia, Pennsylvania. VGX Pharmaceuticals of Blue Bell, Pennsylvania is the exclusive licensee of the application and any patent issuing therefrom. The real party in interest is referred to herein as "Appellants."

(ii) Related Appeals And Interferences

None

(iii) Status Of Claims

The present application was originally filed December 11, 2003, with claims 1-13.

A Preliminary Amendment and Response to Restriction Requirement was filed January 30, 2006 in which claims 6-13 were canceled and new claims 14-28 were added, whereupon claims 1-5 and 14-28 were pending.

A Response and Amendment was filed August 16, 2006 in response to a Non-Final Rejection of the claims, in which claims 19, 24 and 28 were canceled and new claims 29-34 were added, whereupon claims 1-5, 14-18, 20-23, 25-27 and 29-34 were pending.

A Reply and Amendment was filed April 30, 2007 in response to a Final Rejection of the claims, requesting that claims 1-5, 14-18, 20, 25-27 and 29-31 be canceled.

An Advisory Action dated June 13, 2007 indicated in Item 7 that for purposes of appeal, the proposed amendment would be entered.

Accordingly, claims 21-23 and 32-34 are pending and rejected, and claims 1-20 and 24-31 are canceled. The rejection of claims 21-23 and 32-34 is being appealed.

Claims 21-23 and 32-34, which are at issue in this appeal, appear in the Claims Appendix.

(iv) Status Of Amendments

A Reply and Amendment was filed April 30, 2007 in response to a Final Rejection of the claims, requesting that claims 1-5, 14-18, 20, 25-27 and 29-31 be canceled.

An Advisory Action dated June 13, 2007 indicated in Item 7 that for purposes of appeal, the proposed amendment would be entered.

(v) Summary of Claimed Subject Matter

There are 2 independent claims pending in the present application: claims 21 and 32. Claims 22 and 23 are dependent on claim 21 and claims 33 and 34 are dependent on claim 32

Claim 21 relates to methods of preventing lymphocyte activation. The method comprises the steps of obtaining isolated Vpr protein and contacting the lymphocytes with an amount of the Vpr protein effective to prevent activation. Support for claim 21 can be found in claim 4 as originally filed and in the specification, such as, for example, at page 7, lines 16-26; page 9, lines 11-14, page 10, lines 16-20 and 27-34, and page 11, lines 3-8.

Claim 22 is dependent on claim 21 and relates to methods of claim 21 in which the lymphocytes are T cells.

Claim 23 is dependent on claim 21 and relates to methods of claim 21 in which the lymphocytes are B cells.

Claim 32 relates to methods of inhibiting lymphocyte activation. The method comprises the steps of obtaining isolated Vpr protein and contacting the lymphocytes with an amount of the Vpr protein effective to inhibit activation wherein cytokine production and secretion that occurs due to lymphocyte activation by immunoglobulin is inhibited. Support for claim 32 can be found in the specification, such as, for example, at page 10, lines 14-20.

Claim 33 is dependent on claim 32 and relates to methods of claim 32 in which the lymphocytes are T cells.

Claim 34 is dependent on claim 32 and relates to methods of claim 32 in which the lymphocytes are B cells.

(vi) Grounds of Rejection to be Reviewed on Appeal

There are grounds of rejection to be reviewed on appeal:

1) whether the rejection of claims 21-23 as being unpatentable under 35 U.S.C. § 103(a), as allegedly being obvious over Rogel, was erroneous; and

2) whether the rejection of claims 32-34 as being unpatentable under 35 U.S.C. § 103(a), as allegedly being obvious over Rogel, was erroneous.

(vii) Argument

A. Claims 21-23

1. Introduction

The rejection of claims 21-23 as being unpatentable under 35 U.S.C. § 103(a over Rogel was erroneous because the subject matter of the claims would not have been obvious to one skilled in the art in view of Rogel. Rogel refers to the inhibition of lymphocyte proliferation using HIV virus strains and pseudotypes and inhibition of proliferation of non-lymphocyte cells using expression constructs which encode Vpr protein. On the other hand, the claimed subject matter refers to the prevention of lymphocyte activation by contacting lymphocytes with an amount of Vpr protein effective to prevent lymphocyte activation. Rogel does not disclose or mention lymphocyte activation, much less suggest Vpr protein preventing lymphocyte activation. In view of the teachings in Rogel, one skilled in the art would not have concluded that lymphocyte activation could be prevented by obtaining isolated Vpr protein and contacting lymphocytes with an amount of the Vpr protein effective to prevent lymphocyte activation.

2. Controlling Law

The law regarding obviousness fully supports Appellants' position. In *Graham* v. *John Deere Co. of Kansas City,* 383 U.S. 1, 148 U.S.P.Q. 459 (1966), the Court set out a framework for applying the statutory language of §103, language itself based on the logic of the earlier decision in *Hotchkiss v. Greenwood*, 11 How. 248 (1851), and its progeny. *See KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1734, 82 U.S.P.Q.2d 1385 (2007). It is an objective analysis:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. *See Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 U.S.P.Q. 459 (1966).

It is well settled that *Graham v. John Deere Co.* is to be followed in the consideration and determination of obviousness under 35 U.S.C. § 103. In doing so, four factual inquires are made:

(1) Determining the scope and contents of the prior art;

(2) Ascertaining the differences between the prior art and the claims in issue;

(3) Resolving the level of ordinary skill in the pertinent art; and

(4) Evaluating evidence of secondary considerations.

The scope and content of the prior art includes references in the field of applicant's endeavor as well as those reasonably pertinent to the particular problem with which the inventor is concerned. *Wang Lab., Inc.* v. *Toshiba Corp.,* 993 F.2d 858, 864, 26 U.S.P.Q.2d 1767, 1773 (Fed. Cir. 1993); *In re Clay,* 966 F.2d 656, 658-659, 23 U.S.P.Q.2d 1058, 1060 (Fed. Cir. 1992) ("A reference is reasonably pertinent if, even though it may be in a different field from that of the inventor's endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem."); *In re Oetiker,* 977 F.2d 1443, 1447, 24 U.S.P.Q.2d 1443, 1445 (Fed. Cir. 1992); *In re Deminski,* 796 F.2d 436, 442, 230 U.S.P.Q. 313, 315 (Fed. Cir. 1986).

The Patent and Trademark Office determines the scope of claims in patent applications not solely on the basis of the claim language, but upon giving claims their broadest reasonable construction "in light of the specification as it would be interpreted by one of ordinary skill in the art." *In re Am. Acad. of Sci. Tech. Ctr.*, 367 F.3d 1359, 1364, 70 USPQ2d 1827 (Fed. Cir. 2004). "The PTO applies to language of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification." *In re Morris*, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997). The broadest reasonable interpretation of the claims must be consistent with the interpretation that those skilled in the art would reach. *In re Cortright*, 165 F.3d 1353, 1359, 49 USPQ2d 1464, 1468 (Fed. Cir. 1999).

When applying 35 U.S.C. § 103, the following basic considerations of law must be adhered to: (1) the claimed invention must be considered as a whole; (2) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (3) the references must be viewed without the benefit of impermissible hindsight

vision afforded by the claimed invention, and (4) reasonable expectation of success is the standard with which obviousness is determined. *Hodosh* v. *Block Drug Co.,* 786 F.2d 1136, 1143 n.5, 229 U.S.P.Q. 182, 187 n.5 (Fed. Cir. 1986), *cert, denied,* 479 U.S. 827 (1986).

Rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *KSR Int'l Co. v. Teleflex Inc*., *Supra* at 1396.

As a matter of procedure, to properly reject a claim as being obvious in view of the prior art, the Examiner has the initial burden of establishing a case of *prima facie* obviousness. *In re Oetiker,* 977 F.2d at 1445; *In re Piasecki,* 745 F.2d 1468, 1472, 223 U.S.P.Q. 785, 788 (Fed. Cir. 1984). The legal concept of *prima facie* obviousness is a procedural tool of examination which applies broadly to all arts. *In re Oetiker,* 911 F.2d at 1445; *In re Rinehart,* 531 F.2d 1048, 1052, 189 U.S.P.Q. 143, 147 (CCPA 1976). It allocates who has the burden of going forward with production of evidence in each step of the examination process. *Id.* The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. *In re Oetiker,* 977 F.2d at 1445; *In re Piasecki,* 745 F.2d at 1472. If the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness. *In re Oetiker,* 977 F.2d at 1445.

To establish *a prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Vaeck,* 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Second, there must be a reasonable expectation of success. *Id.* Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *Id.*

The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. Obviousness does not require absolute

predictability; however, at least some degree of predictability is required. *In re Merck & Co.,* 800 F.2d 1091, 1097 (Fed. Cir. 1986).

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988).

The ultimate determination of patentability is based on the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence. *In re Oetiker,* 977 F.2d at 1445. The legal standard of "a preponderance of evidence" requires the evidence to be more convincing than the evidence which is offered in opposition to it. With regard to rejections under 35 U.S.C. § 103, the examiner must provide evidence which as a whole shows that the legal determination sought to be proved (i.e., the reference teachings establish a *prima facie* case of obviousness) is more probable than not.

3. Relevant facts

Claims 21-23 refer to methods of preventing lymphocyte activation. The steps set forth in independent claim 21 include the step of "obtaining isolated Vpr protein" and the step of

> contacting lymphocyte cells with an amount of said Vpr protein effective to prevent activation.

In describing the methods, the specification clearly discloses that Vpr prevents lymphocyte activation as well as cell proliferation. For example, on page 9 lines 11-14 of the specification states:

> It has been discovered that HIV protein vpr inhibits cell proliferation, induces undifferentiated cells to differentiate, that vpr effects modifies the state of macrophage cells, and prevents activation of lymphocytes.

On page 10, lines 14-20, the specification clearly describes what happens when activation is inhibited or prevented, stating

> It has been discovered that activation of lymphocytes such as T cells B cells and monocytes can be inhibited by vpr. Vpr prevents activation of these cells by immunoglobulin molecules. Activation of these cells by immunoglobulin molecules results in cytokine production/secretion. Accordingly, vpr inhibits cytokine production/secretion by these cells due to immunoglobulin activation.

In the Official Action dated February 16, 2006, the claims were rejected under 35 U.S.C. 102 as anticipated by Rogel. The Office incorrectly characterized the invention on page 5, stating that the "[i]nstant claims are related to a method of inhibiting proliferation of cells…"

Rogel discloses data comparing cell proliferation of HIV-infected lymphocyte cell lines when infected with HIV strains comprising wild-type or *vpr*$^-$ mutations. Rogel discloses that populations of lymphocyte cell lines infected with *vpr*$^-$ HIV strains only recovered following initial death of a large proportion of infected cells. Rogel also discloses comparing cell proliferation of PBMCs infected with HIV pseudotypes that were either *vpr*$^+$ or *vpr*$^-$. Rogel additionally compares proliferation of 293T cells, a human embryonic kidney cell line, transfected with an expression vector encoding Vpr, and shows that Vpr expression inhibits proliferation of the cells.

Rogel makes no mention of lymphocyte activation or secretion of cytokines in response to activation signals. Rather, Rogel is focused upon Vpr's effect on cell proliferation and the cell cycle. Moreover, in experiments using T cells, Rogel uses HIV virus or HIV pseudotypes, not isolated protein or genes in expression vectors. The only experiments which singularly test Vpr are those that include expression of Vpr in non-lymphocyte cells.

In Appellants' response filed August 16, 2006, Appellants pointed out on page 9 that Rogel *et al.* does not teach or suggest the effect of Vpr on lymphocyte activation, nor does Rogel *et al.* teach or suggest administering Vpr to lymphocytes to prevent or inhibit lymphocyte activation.

In the Official Action dated October 31, 2006, the claims were rejected under 35 U.S.C. 103 as obvious in view of Rogel. The Office restated the incorrect characterization of the invention stated in the earlier Official Action, stating on page 3 that "[t]he instant invention is a method of inhibiting proliferation of cells…"

In Appellants' response filed April 30, 2007, Appellants pointed out the following on page 5:

> Rogel does not disclose obtaining isolated Vpr protein. Rogel does not disclose contacting lymphocyte cells with an amount of the Vpr protein effective to prevent activation. Rogel does not disclose contacting lymphocyte cells with an amount of the Vpr protein effective to inhibit activation, such that cytokine production and secretion of immunoglobulin by lymphocyte cells are inhibited. Rogel is completely silent with regard to lymphocyte activation, cytokine production, and cytokine secretion. Rogel neither teaches nor suggests any effect of Vpr protein on the activation of infected lymphocyte populations.
>
> Applicants contend that the invention was not *prima facie* obvious at the time of the invention. The invention relates to lymphocyte activation. Rogel is silent with respect to lymphocyte activation. It would not be obvious for one skilled in the art at the time of the invention to make or use the claimed invention. Accordingly, the Office has not established a *prima facie* case for obviousness.
>
> The claims are not *prima facie* obvious.

In the Advisory Action dated June 13, 2007, the Office stated on page 2 that the amendment dated April 30, 2007 did not place the application in condition for allowance because:

> Applicants' arguments regarding the 103 rejection have been carefully considered and are not persuasive. Applicants argue that Rogel does not disclose contacting lymphocyte cells with the isolated Vpr protein effective to inhibit activation,

> such that cytokine production and secretion of immunoglobulin by lymphocyte cells are inhibited. Although Rogel does not specifically describe the biological mechanism of inhibition of lymphocyte activation, Rogel disclose the method step of contacting lymphocyte cells with HIV expressing the Vpr protein, which would necessarily have the effect of inhibition of lymphocyte activation. Since the method steps are obvious over Rogel *et al.*, it appears that the prior art method discloses the property of preventing or inhibiting lymphocyte activation, absent evidence to the contrary. Applicants need to provide evidence showing that the claimed invention is distinguished over the prior art.

There is nothing in the record that suggests that the ordinary meanings of "activation" and "proliferation" as understood by those skilled in the art are interchangeable and no such assertion has been made by the Office. On the contrary, the record fully supports the conclusion that usage is not interchangeable and that the two terms, "lymphocyte activation" and "lymphocyte proliferation," are recognized by those skilled in the art as not being interchangeable.

4. Analysis

One of ordinary skill in the art would not conclude that the claimed subject matter, a method of preventing lymphocyte activation by contacting lymphocytes with an amount of Vpr protein effective to prevent lymphocyte activation, is obvious in view of Rogel's disclosure.

The subject matter of claims 21-23 is not disclosed or suggested in Rogel, and, thus, the rejection of claims 21-23 as unpatentable under 35 U.S.C. § 103(a) over Rogel is erroneous. Rogel does not disclose or mention lymphocyte activation, much less suggest Vpr protein having any effect on lymphocyte activation. Therefore, the methods of preventing lymphocyte activation using Vpr protein would not have been obvious to one skilled in the art in view of Rogel.

The claims specifically require that lymphocyte cells be contacted with isolated Vpr protein in an amount effective to prevent activation of the lymphocytes. Such a step would not

have been obvious to one skilled in the art based upon the teachings in Rogel. Rogel does not teach or suggest that Vpr has any effect on the activation of lymphocytes, which involves the production and secretion of cytokines. Nothing in Rogel suggests prevention of lymphocyte activation by contacting lymphocytes with an amount of isolated Vpr protein effective to prevent activation.

The Advisory Action recognizes the difference between lymphocyte proliferation and lymphocyte activation and acknowledges that Rogel does not describe lymphocyte activation. In explaining why the rejection is maintained, the Advisory Action indicates that Rogel's disclosure of contacting lymphocyte cells with HIV that expresses Vpr would necessarily inhibit lymphocyte activation thereby rendering the claim invention obvious.

This logic is flawed. First, Rogel did not disclose any effect on lymphocyte activation. The claimed invention involving the step of contacting lymphocytes with an amount of Vpr protein effective to prevent lymphocyte activation could not be obvious when Rogel fails to recognize this effect on lymphocyte activation. Moreover, one skilled in the art could not conclude with a reasonable expectation of success that an amount of Vpr protein effective to prevent lymphocyte activation could be contacted with lymphocyte cells to prevent lymphocyte activation based upon experiments performed on lymphocyte cell lines and PBMCs using HIV virus and pseudotype strains.

Rogel does not report any data on or mention lymphocyte activation. The experiments in Rogel using lymphocyte cell lines and PBMCs used Vpr^+ and Vpr^- HIV virus and pseudotype strains which contain other HIV genes. These experiments do not render obvious claims to methods of preventing lymphocyte activation that comprise the steps of obtaining Vpr protein and contacting lymphocytes with an amount of the Vpr protein effective to prevent lymphocyte activation. The experiments in Rogel in which Vpr is tested without other HIV genes were performed on non-lymphocyte cells.

There is no disclosure that Vpr prevents lymphocyte activation, and accordingly no disclosure of contacting lymphocyte cells with an amount of Vpr effective to prevent lymphocyte activation.

There is no suggestion or motivation in Rogel and the knowledge generally available to one of ordinary skill in the art, that Vpr can be used to prevent lymphocyte activation. One skilled in the art, reviewing the data in Rogel related to the inhibition of cell proliferation of lymphocyte cell lines and PBMCs using HIV virus strains and pseudotypes, and on inhibition of cell proliferation of non-lymphocyte cell lines using expression constructs that encode Vpr protein would not have been motivated to prevent lymphocyte activation by contacting lymphocyte cells with Vpr in an effective amount to prevent lymphocyte activation. Moreover, to the extent they would attempt to do so, there would be no reasonable expectation of success. Rogel does not teach or suggest that Vpr prevents lymphocyte activation.

One skilled in the art would not conclude that the claimed invention is *prima facie* obvious in view of Rogel. The rejection of claims 21-23 as being obvious in view of Rogel is erroneous.

5. Conclusion

For the forgoing reasons, Appellants respectfully request that the rejection of claims 21-23 as being unpatentable under 35 U.S.C. § 103(a), as allegedly being obvious over Rogel, be reversed.

B. Claims 32-34

1. Introduction

The rejection of claims 32-34 as being unpatentable under 35 U.S.C. § 103(a), as allegedly being obvious over Rogel, was erroneous because the subject matter of the claims would not have been obvious to one skilled in the art in view of Rogel. Rogel refers to the inhibition of lymphocyte proliferation using HIV virus strains and pseudotypes and inhibition of proliferation of non-lymphocyte cells using expression constructs which encode Vpr protein. The claimed subject matter refers to the inhibition of lymphocyte activation by contacting lymphocytes with an amount of Vpr protein effective to inhibit lymphocyte activation and specifically recites that such cytokine production and secretion by immunoglobulin activation of lymphocyte cells is inhibited. Rogel does not disclose or mention lymphocyte activation, much

less suggest Vpr protein having any effect on it. In contrast, Rogel fails to disclose or mention cytokine production and secretion. In view of the limited teachings in Rogel, one skilled in the art would not conclude that lymphocyte activation can be inhibited by obtaining isolated Vpr protein and contacting lymphocytes with an amount of the Vpr protein effective to inhibit lymphocyte activation wherein cytokine production and secretion by immunoglobulin activation of lymphocyte cells is inhibited.

2. Controlling Law

The law regarding obviousness fully supports Appellants' position. In *Graham* v. *John Deere Co. of Kansas City,* 383 U.S. 1, 148 U.S.P.Q. 459 (1966), the Court set out a framework for applying the statutory language of §103, language itself based on the logic of the earlier decision in *Hotchkiss v. Greenwood*, 11 How. 248 (1851), and its progeny. *See KSR Int'l Co. v. Teleflex Inc*., 127 S. Ct. 1727, 1734, 82 U.S.P.Q.2d 1385 (2007). It is an objective analysis:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. *See Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 U.S.P.Q. 459 (1966).

It is well settled that *Graham v. John Deere Co.* is to be followed in the consideration and determination of obviousness under 35 U.S.C. § 103. In doing so, four factual inquires are made:

(1) Determining the scope and contents of the prior art;

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(3) Resolving the level of ordinary skill in the pertinent art; and

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The scope and content of the prior art includes references in the field of applicant's endeavor as well as those reasonably pertinent to the particular problem with which the inventor is concerned. *Wang Lab., Inc.* v. *Toshiba Corp.,* 993 F.2d 858, 864, 26 U.S.P.Q.2d 1767, 1773 (Fed. Cir. 1993); *In re Clay,* 966 F.2d 656, 658-659, 23 U.S.P.Q.2d 1058, 1060 (Fed. Cir. 1992)

("A reference is reasonably pertinent if, even though it may be in a different field from that of the inventor's endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem."); *In re Oetiker,* 977 F.2d 1443, 1447, 24 U.S.P.Q.2d 1443, 1445 (Fed. Cir. 1992); *In re Deminski,* 796 F.2d 436, 442, 230 U.S.P.Q. 313, 315 (Fed. Cir. 1986).

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When applying 35 U.S.C. § 103, the following basic considerations of law must be adhered to: (1) the claimed invention must be considered as a whole; (2) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention, and (4) reasonable expectation of success is the standard with which obviousness is determined.*Hodosh* v. *Block Drug Co.,* 786 F.2d 1136, 1143 n.5, 229 U.S.P.Q. 182, 187 n.5 (Fed. Cir. 1986), *cert, denied,* 479 U.S. 827 (1986).

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As a matter of procedure, to properly reject a claim as being obvious in view of the prior art, the Examiner has the initial burden of establishing a case of *prima facie* obviousness. *In re*

Oetiker, 977 F.2d at 1445; *In re Piasecki,* 745 F.2d 1468, 1472, 223 U.S.P.Q. 785, 788 (Fed. Cir. 1984). The legal concept of *prima facie* obviousness is a procedural tool of examination which applies broadly to all arts. *In re Oetiker,* 911 F.2d at 1445; *In re Rinehart,* 531 F.2d 1048, 1052, 189 U.S.P.Q. 143, 147 (CCPA 1976). It allocates who has the burden of going forward with production of evidence in each step of the examination process. *Id.* The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. *In re Oetiker,* 977 F.2d at 1445; *In re Piasecki,* 745 F.2d at 1472. If the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness. *In re Oetiker,* 977 F.2d at 1445.

To establish *a prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Vaeck,* 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Second, there must be a reasonable expectation of success. *Id.* Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *Id.*

The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. Obviousness does not require absolute predictability; however, at least some degree of predictability is required. *In re Merck & Co.,* 800 F.2d 1091, 1097 (Fed. Cir. 1986).

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The ultimate determination of patentability is based on the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence. *In re Oetiker,* 977 F.2d at 1445. The legal standard of "a preponderance of evidence" requires the evidence to be more convincing than the evidence which is offered in opposition to it. With regard to rejections under 35 U.S.C. § 103, the examiner must provide evidence which as a whole shows that the legal determination sought to be proved (i.e., the reference teachings establish a *prima facie* case of obviousness) is more probable than not.

3. Relevant facts

Claims 32-34 refer to methods of inhibiting lymphocyte activation. The steps set forth in independent claim 32 include the step of "obtaining isolated Vpr protein" and the step of

> contacting lymphocyte cells with an amount of said Vpr protein effective to inhibit activation; wherein cytokine production and secretion by immunoglobulin activation of lymphocyte cells is inhibited.

In describing the methods, the specification clearly discloses that Vpr prevents lymphocyte activation as well as cell proliferation. For example, on page 9 lines 11-14 of the specification states:

> It has been discovered that HIV protein vpr inhibits cell proliferation, induces undifferentiated cells to differentiate, that vpr effects modifies the state of macrophage cells, and prevents activation of lymphocytes.

On page 10, lines 14-20, the specification clearly describes what happens when activation is inhibited or prevented, stating

> It has been discovered that activation of lymphocytes such as T cells B cells and monocytes can be inhibited by vpr. Vpr prevents activation of these cells by immunoglobulin molecules. Activation of these cells by immunoglobulin molecules results in cytokine production/secretion. Accordingly, vpr inhibits cytokine

> production/secretion by these cells due to immunoglobulin activation.

In the Official Action dated February 16, 2006, the claims were rejected under 35 U.S.C. 102 as anticipated by Rogel. The Office incorrectly characterized the invention on page 5, stating that the "[i]nstant claims are related to a method of inhibiting proliferation of cells…"

Rogel discloses data comparing cell proliferation of HIV-infected lymphocyte cell lines when infected with HIV strains comprising wild-type or *vpr*$^-$ mutations. Rogel discloses that populations of lymphocyte cell lines infected with *vpr*$^-$ HIV strains only recovered following initial death of a large proportion of infected cells. Rogel also discloses comparing cell proliferation of PBMCs infected with HIV pseudotypes that were either *vpr*$^+$ or *vpr*$^-$. Rogel additionally compares proliferation of 293T cells, a human embryonic kidney cell line, transfected with an expression vector encoding Vpr, and shows that Vpr expression inhibits proliferation of the cells.

Rogel makes no mention of lymphocyte activation or secretion of cytokines in response to activation signals. Rather, Rogel is focused upon Vpr's effect on cell proliferation and the cell cycle. Moreover, in experiments using T cells, Rogel uses HIV virus or HIV pseudotypes, not isolated protein or genes in expression vectors. The only experiments which singularly test Vpr are those that include expression of Vpr in non-lymphocyte cells.

In Appellants' response filed August 16, 2006, Appellants pointed out on page 9 that Rogel *et al*. does not teach or suggest the effect of Vpr on lymphocyte activation, nor does Rogel *et al*. teach or suggest administering Vpr to lymphocytes to prevent or inhibit lymphocyte activation.

In the Official Action dated October 31, 2006, the claims were rejected under 35 U.S.C. 103 as obvious in view of Rogel. The Office restated on page 3 the incorrect characterization of the invention stated in the earlier Official Action, stating that "[t]he instant invention is a method of inhibiting proliferation of cells…"

In Appellants' response filed April 30, 2007, Appellants pointed out the following on page 5:

> Rogel does not disclose obtaining isolated Vpr protein. Rogel does not disclose contacting lymphocyte cells with an amount of the Vpr protein effective to prevent activation. Rogel does not disclose contacting lymphocyte cells with an amount of the Vpr protein effective to inhibit activation, such that cytokine production and secretion of immunoglobulin by lymphocyte cells are inhibited. Rogel is completely silent with regard to lymphocyte activation, cytokine production, and cytokine secretion. Rogel neither teaches nor suggests any effect of Vpr protein on the activation of infected lymphocyte populations.
>
> Applicants contend that the invention was not *prima facie* obvious at the time of the invention. The invention relates to lymphocyte activation. Rogel is silent with respect to lymphocyte activation. It would not be obvious for one skilled in the art at the time of the invention to make or use the claimed invention. Accordingly, the Office has not established a *prima facie* case for obviousness.
>
> The claims are not *prima facie* obvious.

In the Advisory Action dated June 13, 2007, the Office stated on page 2 that the amendment dated April 30, 2007 did not place the application in condition for allowance because:

> Applicants' arguments regarding the 103 rejection have been carefully considered and are not persuasive. Applicants argue that Rogel does not disclose contacting lymphocyte cells with the isolated Vpr protein effective to inhibit activation, such that cytokine production and secretion of immunoglobulin by lymphocyte cells are inhibited. Although Rogel does not specifically describe the biological mechanism of inhibition of lymphocyte activation, Rogel disclose the method step of contacting lymphocyte cells with HIV expressing the Vpr protein, which would necessarily have the effect of inhibition of lymphocyte activation. Since the method steps are obvious over Rogel *et al.*, it

> appears that the prior art method discloses the property of preventing or inhibiting lymphocyte activation, absent evidence to the contrary. Applicants need to provide evidence showing that the claimed invention is distinguished over the prior art.

There is nothing in the record that suggests that the ordinary meanings of "activation" and "proliferation" as understood by those skilled in the art are interchangeable and no such assertion has been made by the Office. On the contrary, the record fully supports the conclusion that usage is not interchangeable and that the two terms, "lymphocyte activation" and "lymphocyte proliferation," are recognized by those skilled in the art as not being interchangeable.

4. Analysis

One of ordinary skill in the art would not conclude that the claimed subject matter, a method of inhibiting lymphocyte activation by contacting lymphocytes with an amount of Vpr protein effective to inhibit lymphocyte activation wherein cytokine production and secretion by immunoglobulin activation of lymphocyte cells is inhibited, is obvious in view of Rogel's disclosure.

The subject matter of claims 32-34 is not disclosed or suggested in Rogel and the rejection of claims 32-34 as being unpatentable under 35 U.S.C. § 103(a) over Rogel is erroneous. Rogel does not disclose or mention lymphocyte activation, much less suggest Vpr protein having any effect on it. Methods of inhibiting lymphocyte activation using Vpr protein would not have been obvious to one skilled in the art in view of Rogel.

The claims specifically require that lymphocyte cells be contacted with isolated Vpr protein in an amount effective to inhibit activation of the lymphocytes wherein cytokine production and secretion by immunoglobulin activation of lymphocyte cells is inhibited. Such a step would not have been obvious to one skilled in the art based upon the teachings in Rogel. Rogel does not teach or suggest that Vpr has any effect on the activation of lymphocytes, which involves the production and secretion of cytokines. Nothing in Rogel suggests inhibition of lymphocyte activation by contacting lymphocytes with an amount of isolated Vpr protein

effective to inhibit activation wherein cytokine production and secretion by immunoglobulin activation of lymphocyte cells is inhibited.

The Advisory Action recognizes the difference between lymphocyte proliferation and lymphocyte activation and acknowledges that Rogel does not describe lymphocyte activation. In explaining why the rejection is maintained, the Advisory Action indicates that Rogel's disclosure of contacting lymphocyte cells with HIV that expresses Vpr would necessarily inhibit lymphocyte activation thereby rendering the claim invention obvious.

This logic is flawed. First, Rogel did not disclose any effect on lymphocyte activation. The claimed invention involving the step of contacting lymphocytes with an amount of Vpr protein effective to inhibit lymphocyte activation could not be obvious when Rogel fails to recognize this effect on lymphocyte activation. Moreover, one skilled in the art could not conclude with a reasonable expectation of success that an amount of Vpr protein effective to inhibit lymphocyte activation could be contacted with lymphocyte cells to inhibit lymphocyte activation based upon experiments performed on lymphocyte cell lines and PBMCs using HIV virus and pseudotype strains.

Rogel does not report any data on or mention lymphocyte activation. The experiments in Rogel using lymphocyte cell lines and PBMCs used Vpr^+ and Vpr^- HIV virus and pseudotype strains which contain other HIV genes. These experiments do not render obvious claims to methods of inhibiting lymphocyte activation that comprise the steps of obtaining Vpr protein and contacting lymphocytes with an amount of the Vpr protein effective to inhibit lymphocyte activation wherein cytokine production and secretion by immunoglobulin activation of lymphocyte cells is inhibited. The experiments in Rogel in which Vpr is tested without other HIV genes were performed on non-lymphocyte cells.

There is no disclosure that Vpr prevents lymphocyte activation, and accordingly no disclosure of contacting lymphocyte cells with an amount of Vpr effective to prevent lymphocyte activation.

There is no suggestion or motivation in Rogel and the knowledge generally available to one of ordinary skill in the art, that Vpr can be used to inhibit lymphocyte activation. One

skilled in the art, reviewing the data in Rogel on the inhibition of cell proliferation of lymphocyte cell lines and PBMCs using HIV virus strains and pseudotypes, and on inhibition of cell proliferation of non-lymphocyte cell lines using expression constructs that encode Vpr protein would not have been motivated to inhibit lymphocyte activation by contacting lymphocyte cells with Vpr in an effective amount to inhibit lymphocyte activation wherein cytokine production and secretion by immunoglobulin activation of lymphocyte cells is inhibited. Moreover, to the extent they would attempt to do so, there would be no reasonable expectation of success. Rogel does not teach or suggest that Vpr inhibits lymphocyte activation.

One skilled in the art would not conclude that the claimed invention is *prima facie* obvious in view of Rogel. The rejection of claims 32-34 as being obvious in view of Rogel is erroneous.

5. Conclusion

For the forgoing reasons, Appellants respectfully request that the rejection of claims 32-34 as being unpatentable under 35 U.S.C. § 103(a), as allegedly being obvious over Rogel, be reversed.

C. Summary

For the foregoing reasons, Appellants respectfully urge that the rejection of claims 21 – 23 and 32 – 34 under 35 U.S.C. § 103(a) be reversed.

Respectfully submitted,

/Mark DeLuca, Reg. No. 33,229/

Mark DeLuca, Reg. No. 33,229

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PEPPER HAMILTON LLP
400 Berwyn Park
899 Cassatt Road
Berwyn, PA 19312
(610) 640-7855 (Telephone)
(610) 640-7835 (Facsimile)

(viii) Claims Appendix

The following claims are at issue in this appeal.

1. – 20. (Canceled).

21. A method of preventing lymphocyte activation which comprises the steps of:

obtaining isolated Vpr protein; and

contacting lymphocyte cells with an amount of said Vpr protein effective to prevent activation.

22. The method of claim 21 wherein said lymphocyte cells are T cells.

23. The method of claim 21 wherein said lymphocyte cells are B cells.

24.– 31. (Canceled).

32. A method of inhibiting lymphocyte activation which comprises the steps of:

obtaining isolated Vpr protein; and

contacting lymphocyte cells with an amount of said Vpr protein effective to inhibit activation;

wherein cytokine production and secretion by immunoglobulin activation of lymphocyte cells is inhibited.

33. The method of claim 32 wherein said lymphocyte cells are T cells.

34. The method of claim 32 wherein said lymphocyte cells are B cells.

(ix) Evidence Appendix

None.

(x) Related Proceedings Appendix

None.